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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,801	03/13/2001	Mary Collins	GNN-016	2860

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,801	COLLINS ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 9/9/04, has been entered.
Claim 2 has been canceled.
Claims 1, 3, 4 and 5 have been amended.

Claims 1 and 3-5 are pending and being acted upon as they read on the election species

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 9/9/04.
The rejections of record can be found in the previous Office Action.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Upon reconsideration of applicant's amended claims to recited "consisting essentially of" rather than "consisting of", the previous rejection under 35 U.S.C. § 102(e) has been re-instated.

For examination purposes, the recitation of "consisting essentially of" is interpreted to be open the same as "comprising". Therefore, the recitation of "consisting essentially of" reads on the inclusion of other ingredients and method steps, including even in major amounts. See MPEP 2111.03.

6. Claims 1 and 3-5 are rejected under 35 U.S.C. § 102(e) as being anticipated by Sayegh et al. (U.S. Patent No. 6,280,957 (see entire document) essentially for the reasons of record and reiterated herein for applicant's convenience.

For examination purposes, the recitation of "consisting essentially of" is interpreted to be open the same as "comprising". Therefore, the recitation of "consisting essentially of" reads on the inclusion of other ingredients and method steps, including even in major amounts. See MPEP 2111.03.

Sayegh et al. teach methods of transplanting grafts, including intestines (see columns 3-4, overlapping paragraph), with blockers of the CD28-B7 interactions, including anti-B7-1 and/or anti-B7-2 antibodies (see column 1, lines 55-61; column 3, lines 45-48) and immunosuppessive agents capable of inactivating T cells, including rapamycin (see column 4, paragraph 2). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to transplant intestines with combination therapies, including the use of anti-B7-1 and anti-B7-2 antibodies and rapamycin.

Given the breadth of the instant claims, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.

In contrast to applicant's assertions; disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi USPQ 423 (CCPA 1971). A known or obvious composition does not patentable simply because it has been described as somewhat inferior to some other product for the same use. See In re Gurley 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See MPEP 2123.

Applicant's arguments are not found persuasive.

7. Claims 1 and 3-5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent No. 5,869,050) in view of Lenschow et al. (Transplantation 60: 1171-1178, 1995), Tarumi et al. (Transplantation 67: 520-525, 1999) AND/OR Newell et al. (J. Immunol. 163: 2358-2362, 1999) and in further view of
Chen et al. (Transplantation 59: 1084 – 1089), Strom et al. (Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, pages 451-456) and Li et al. (Transplantation 66: 1387 – 1388 (1998) essentially for the reasons of record.

Applicant's arguments, filed 9/9/04, have been fully considered but are not found convincing essentially for the reasons of record.

Again applicant continues to argue that both the suggestion and the reasonable expectation of success must be founded in the prior art and not in applicant's disclosure, which is not satisfied by the prior art of record.

Applicant agues that the ordinary artisan would not have been motivated to specifically target signaling by B7-1 and B7-2 to prolong intestinal allograft transplants.

Citing Yin et al. (Transplantation 62: 1537-1539, 1996) (Appendix B); applicant asserts that the nature of the immune response to intestinal allografts seems to be unique compared to other types of allografts, whereby results obtained from experiments with other types of allografts cannot be extrapolated to transplantation of intestinal grafts.

Applicant argues that both Newell et al. And Tarumi et al. would not have motivated the ordinary artisan to try to prolong intestinal allograft acceptance using antibodies to B7-1 and B7-2, given the limitations of CTLA4Ig on intestinal allograft survival in these references in experimental models

Applicant argues that there would not have been an expectation of success at the time the invention was made, given the distinction between biological processes between intestinal allografts and other allograft tissues / organs, since in the cited prior art CTLA-4, which was known to block both B7-1 and B7-2 induced costimulation, was insufficient to prevent intestinal allograft rejection.

Applicant asserts that present invention is based on a specific analysis of the involvement of B7-1 and B7-2 in intestinal allograft transplant rejection in a highly relevant mouse model system.

As pointed out previously, it is noted that for examination purposes, the claimed methods recite "consisting essentially of" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

The prior art teach combination therapy, including the use of immunosuppressives such as rapamycin the transplantation of allografts, as taught by De Boer et al. which teach the use of B7-specific antibodies to inhibit transplant rejection, including combination therapy with known immunosuppressives such as rapamycin (see columns 6-7, Immunosuppressive Agents; Claims 6, 13) (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims).

Lenschow et al. teach the inhibition of transplant rejection with both B7-1-specific and B7-2-specific antibodies and that maximal inhibition of allogeneic responses was observed with the combination of both B7-1-specific and B7-2-specific antibodies (see entire document, including Abstract, Results and Discussion). It is noted that Lenschow et al. observed while anti-B7-1 antibody therapy had little effect of graft prolongation, a combination of anti-B7-1/anti-B7-2 antibodies significantly prolonged graft survival (see Abstract, Results and Discussion).

Also, Lenschow et al. notes that with in vivo therapy using a combination of anti-B7-1 plus anti-B7-2 monoclonal antibodies significantly prolonged the mean survival time of the grafts beyond either the CTLA-4Ig or anti-B7-2 alone (see page 1175, column 2, lines 33-36, last full sentence). Also, Lenschow et al. teach that it is clear that B7-1 plays a secondary but substantive role in allogeneic responses to islet cells in vivo (page 1176, column 1, lines 3-5).

Therefore, in contrast to applicant's assertions that at best merely teach that anti-B7-01 antibodies may be combined with certain second immunosuppressive agents (e.g. cyclosporine A or anti-B7-2 antibodies), the prior art provided sufficient motivation and expectation of success in combining anti-B7-1 and anti-B7-2 antibodies in inhibiting transplant rejection and that in vivo studies indicated that this combination of anti-B7 antibodies was significantly more effective than CTLA4Ig.

Applicant's reliance on Newell et al. (Am J. Transplantation 3: 1-2, (2003) that intestinal transplants are different from other organs and Kahan et al. (Expert Opin. Pharmacother 2: 1903 (2001) that cyclosporine is not interchangeable with rapamycin is acknowledged.

However, again it is clear that the prior art provide direction and expectation of success in combining anti-B7 antibodies in combination with immunosuppressives such as rapamycin in inhibiting immune responses at the time the invention was made.

In contrast to applicant's arguments, it is noted that Example 1 on pages 44 – 45 of the instant specification notes that "Inhibition of the CD28/B7 pathway delays or prevents allograft rejection in a number of experimental models" and "Inhibition of the CD28/B7 pathway by anti-B7 antibodies or by genetic disruption blocks intestinal allograft rejection more effectively than does mCTLA4Ig suggesting that not all approaches to blocking a costimulatory pathway are equivalent".

These comments disclosed in the specification as filed are consistent with the rejection of record in that given the ability of inhibiting the CD28/B7 pathway in a number of allograft models, one of ordinary skill in the art would have been motivated to inhibit intestinal allografts via the same pathway as well with an expectation of success and that the reagents (e.g. combination of anti-B7-1 and anti-B7-2 antibodies versus CTLA4-Ig) that block the CD28/B7 can differ.

Further, Section IV, Therapeutic Uses of Anti-B7 Antibodies in Inhibition of Immune Responses on pages 36 – 37 of the instant specification discloses a number of assays, including a number of in vitro assays, to test ant ability of anti-B7 antibodies to inhibit immune responses.

Again, applicant's arguments concerning the reliance on in vitro and in vivo model systems in the prior art is inconsistent with applicant's own reliance on such experimental models as well as the clear direction and guidance in the prior art as it reads on the claimed methods of inhibiting rejection of intestinal allografts.

Again, applicant is reminded that the claims of de Boer et al. include methods of treating transplant or GVHD patients with anti-B7 antibodies and immunosuppressive agents. In contrast to applicant's arguments, de Boer et al. is not limited to in vitro assays of testing anti-B7 antibodies.

Again, while there may have been limitations with CTLA4Ig in experimental murine models of intestinal allografts, Tarumi et al. and Newell et al. clearly provided sufficient motivation and expectation of success in targeting B7-1 and B7-2 in the transplantation of intestinal allografts.

Tarumi et al. teach the use of CTLA4Ig which inhibits the CD28:CTLA4-B7 pathway to induce the long-term acceptance of small bowel allografts (see entire document).

Newell et al. also teach the use of CTLA4Ig which blocks the CD28/B7 pathway, resulting in the prevention of intestinal allografts (see entire document).

Further Tarumi et all. teach that clinical bowel transplantation is accompanied by immunosuppression (e.g. see the first paragraph of the Discussion on page 522, column 2) and that a blockade of costimulatory signals were useful for suppression of alloreactive immune responses (e.g. see Discussion on page 522).

While there may be differences in the ability of CTLA4-Ig and antiB7 antibodies in blocking costimulatory pathways in different systems, the prior art again provides sufficient motivation and expectation of success in inhibiting intestinal allograft survival via the CD28/B7 pathway, more particularly with anti-B7-1 and anti-B7-2 antibodies as well as the rapamycin at the time the invention was made.

Again, the claims encompass combined immunosuppression, wherein the combined prior art provides clear motivation and expectation of success in therapeutic regimens of transplantation. In contrast to applicant's assertions, both Tarumi and Newell provide sufficient motivation and expectation of success that targeting both B7-1 and B7-2 would contribute to preventing or inhibiting intestinal graft survival.

While applicant acknowledges the teachings of Chen et al., Strom et al. and Li et al., applicant asserts that these references do not remedy the deficiencies of the prior art above and do provide sufficient motivation and expectation of success in combining anti-B7-1 antibody, anti-B7-2 antibody and rapamycin the in the treatment of intestinal allografts.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Given that CTLA4Ig blocks both B7-1- and B7-2-mediated responses and given that the combination of anti-B7-1 and anti-B7-2 antibodies achieve significant inhibition of allogeneic responses and graft rejection; one of ordinary skill in the art would have been motivated to combine both B7-1-specific and B7-2-specific antibodies to inhibit transplant rejection, including intestinal transplant rejection. Given the teachings of de Boer et al, Lenschow et al., Tarumi et al. and Newell et al., the ordinary artisan would have an expectation of success in prolonging intestinal graft survival by blocking both B7-1- and B7-2-mediated interactions. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the prior art clearly provide sufficient motivation and expectation of success in providing antagonists of the CD28:B7 pathway, including the combination of anti-B7-1 and anti-B7-2 antibodies in combination with immunosuppressives, including rapamycin, to inhibit graft rejection, including intestinal allografts. Here, the prior art faced solving a similar or known problem in the prior art (allograft rejection or more specifically intestinal allograft rejection) would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve this well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

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n contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard; it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ 367 (CCPA 1977); In re Lindell, 155 USPQ 521 (CCPA 1967). The evidence of purported unobvious results of record in this application is insufficient to overcome the inference of fact in this case. Therefore the above claims remain rejected under 35 USC 103 for the reasons above and also those set forth in the previous Office Action.

Applicant's arguments are not found persuasive.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
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December 27, 2004